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Dear readers,

Since 2006, Discussions has celebrated and promoted undergraduate research at Case Western Reserve University and other universities all over the world. As we enter our tenth year as a research publication, I want to take a look at the progress we have made and our goals for the future. Let me first say that it is truly my pleasure to introduce the newest issue of Discussions to you.

Discussions is the Undergraduate Research Journal of Case Western Reserve University. Although based at CWRU, we have become a global presence, partnering with numerous universities and research institutions around the country as well as receiving submissions from countries as far as China, Russia, Nigeria, and Turkey. As of this issue, Discussions has officially received submissions from every continent in the world (not including Antarctica). While Discussions was started by just a few dedicated students, we have grown to become a large organization dedicated to promoting undergraduate research from the best and brightest students.

By taking the time to read this journal, you are promoting Discussions and, in turn, the long hours of research conducted by undergraduates, often without herald or pay. In choosing to read the papers included in this issue of Discussions, you are stepping into an oft-overlooked niche of research, learning about topics to which you may not have been exposed.

If you would like to see your research published in Discussions, visit our website at www.case.edu/discussions or our Facebook page for submission guidelines and more details.

As we continue to grow in size and prestige, I encourage anyone interested in research or the publication process to find ways to get involved with our publication. We accept submissions from around the world and distribute around the country; our organization’s success has increased exponentially in recent years. As we continue to expand, our goal is to supply more students with an outlet through which they can share their passion for research and inquiry. It has taken nearly ten years to get to where we are now, and my hope is that in another ten years we will be able to look back, knowing our dedication to undergraduate research has only grown. Our primary goal, the same goal that encouraged students to form Discussions in 2006, is to become the premier undergraduate research journal in the country.

Finally, I would like to thank Sheila Pedigo, Bethany Pope, and the entire SOURCE office for their continued support.

Thank you for taking the time to read our journal, and I hope you enjoy the fantastic articles within.

Sincerely,

Benjamin Nudelman

Editor-in-Chief, Discussions Research Journal
Faculty Spotlight

“...our coaching studies can show people how to change their leadership methods and behaviors for the better.”

those who participated in the coaching sessions, specific portions of the subjects’ brains were observed to light up. After further analysis, we recognized these parts of the brain as part of the default mode network, which is correlated to the human mind’s openness to ideas, people, and moral concerns. Often, when students are asked about the courses they are taking and how they are performing in those courses, the task-positive network is activated, which causes them to be more analytic, defensive, and closed to new ideas.

We recently received funding to expand these findings by studying leadership effectiveness in a firefighting team. We hypothesize that effective leaders transition between both the default mode and task positive, which we studied previously. If we can show that, then we think our coaching studies can show people how to change their leadership methods and behaviors for the better.

3. What challenges do you face in your current line of research?

Time. I don’t have enough time. The other challenge is the inevitable one of funding. It’s a real struggle to get money. Fortunately here, Provost William A. “Bud” Baeslack III has provost initiative fund, which has been really helpful to us. We’ve even used some of my funds from my endowed chair. Now, we’re starting to bring money in, but it’s still slow.

4. What type of audience to you hope to address through your research?

I’m trying to save the world, literally. My work really focuses on adults, so my work doesn’t address individuals under 25. I think that is a constant process. You have to constantly feel you ought to do rather than what you dream about doing. You have to discern and work toward what you dream about. Probably the first thing I would suggest a young leader is asking oneself, “What do you want out of life?” And I don’t mean “What job do you want?”; it’s really, “What kind of person do you want to be?” I think that, simply having goals can sometimes limit us. When the question is, “What is your dream?” people often think, “What would I like to do and how would I like to be doing it?” When you are 17 or 18, your answer to that question most likely is not fully yours; rather, it may simply be a reflection of what you think your parents or grandparents want for you. But that is what, in my model, is called “ought self.” These are the things you feel you ought to do rather than what you dream about doing. You have to discern and work toward what you dream about. I think that is a constant process. You have to constantly ask, “Is this getting me closer to the person I want to be?”

5. What advice would you offer young, emerging leaders?

A second major theme is recognizing that we do not go through life alone. You need friends, and you need really good friends. So, one of the things we’ve been trying to get money for is a program where we start teaching freshmen a set of techniques, including vision, meditation, yoga, and volunteering. As an important part of that process, we hope to have students gather into study groups of five to eight people, where they can learn specific techniques on how to help each other. The technical title is “peer coaching.” The concept of finding and nurturing close friendships and task-based groups, regardless of how they come about, is extremely helpful and important to each of us.

“...our coaching studies can show people how to change their leadership methods and behaviors for the better.”

ABSTRACT

The increasing level of obesity in the general population of industrialized nations is a major public health concern. While obesity increases morbidity and mortality, increasing body habitus also impacts the utilization and analysis of medical imaging. The purpose of this retrospective pilot study is to compare the diagnostic effectiveness of Computer Aided Diagnosis (CAD) software (OnGuard™ 5.2) in combination with a hardware based bone suppression tool, Dual Energy Subtraction (DES) radiography on thoracic radiographs of patients with varying levels of obesity. Chest radiographs from 30 patients with CT and pathology verified malignant pulmonary nodules (8-34 mm) and 23 CT negative patient controls with different levels of obesity as measured by Body Mass Index (BMI) were utilized for analysis. Twenty-six patients had a normal BMI (18.5-25) and twenty-seven patients were overweight, obese or morbidly obese (OOMO). Computer Aided Diagnostic Software in the Identification of Malignant Pulmonary Nodules in Dual Energy Subtracted Chest Radiographs? A Pilot Study

Nicholas John Novak

VOLUME 11 - ISSUE 2, 2015

ABSTRACT

The increasing level of obesity in the general population of industrialized nations is a major public health concern. While obesity increases morbidity and mortality, increasing body habitus also impacts the utilization and analysis of medical imaging. The purpose of this retrospective pilot study is to compare the diagnostic effectiveness of Computer Aided Diagnosis (CAD) software (OnGuard™ 5.2) in combination with a hardware based bone suppression tool, Dual Energy Subtraction (DES) radiography on thoracic radiographs of patients with varying levels of obesity. Chest radiographs from 30 patients with CT and pathology verified malignant pulmonary nodules (8-34 mm) and 23 CT negative patient controls with different levels of obesity as measured by Body Mass Index (BMI) were utilized for analysis. Twenty-six patients had a normal BMI (18.5-25) and twenty-seven patients were overweight, obese or morbidly obese (OOMO) with a larger BMI value (between 25-47). Test Sensitivity and Specificity, Analysis of Variance (ANOVA), Z test for Equality of Proportions, Spearman’s rank correlation coefficient and the independent sample Student’s t-test were calculated. P-values less than 0.05 were considered significant. Age was not significantly different between the two BMI groups (t=1.26, p=0.26). CAD software Sensitivity =80.0% and Specificity=72.7% in normal BMI patients while for OOMO patients, Sensitivity=83.3%, but Specificity was reduced to 44.4%. The difference in Specificity between the Normal and OOMO patients approached significance (p=0.09) using the one tailed equality of proportions test (Z=1.3). Similarly, in normal patients, BMI and the number of Regions of Interest (ROI) were nearly significantly correlated (p=0.374, p=0.06) while there was no significant correlation between BMI and ROI for OOMO patients, (p=0.3). There was no difference in Sensitivity between the Normal and OOMO groups; however there was likely a clinically significant difference in Specificity between the two groups, if not a statistically significant difference. Obesity appears to cloud the ability of CAD to identify the absence of malignant pulmonary nodules in OOMO patients. A study with a larger number of patients, particularly obese and morbidly obese patients, may provide a more accurate view of this discrepancy

INTRODUCTION

Chest radiography is one of the most commonly used forms of radiologic examination. One of the goals of chest radiography is the identification of malignant pulmonary nodules. Several authors have suggested that Computer Aided Detection (CAD) may help radiologists to detect cancerous pulmonary nodules (Li, Engelmann, Metz, Doi, &
Research

MacMahon, 2008; Oda et al., 2009). CAD identifies Regions of Interest (ROI) on chest radiographs as areas suspected to be malignant. These ROI are identified as circles imposed on the radiograph. However, high numbers of false positives identified by early versions of CAD software on standard postero-anterior (PA) chest images limited the clinical utility of this technology (Bley et al., 2008; Kasai, Li, Shirahashi, & Doi, 2008; Kohayashi, Xu, MacMahon, Metz, & Doi, 1996). Meizane et al. (2011) indicated that CAD software improved recall rates and diagnostic accuracy, particularly in cases with small pulmonary nodules or inexperienced readers. Other researchers (Monnier-Cholley, Carrat, Cholley, Tubiana, & Arrive, 2004; Shah et al., 2005) determined that a large proportion of the false positives and missed lung cancer cases occurred because of bony structures in the chest, in particular clavicles and rib crossings. The literature on the subject suggests that the use of bone suppression improves the diagnostic accuracy of digital chest radiography. Many authors advocate the suppression of ribs and clavicles in digital chest images to improve malignant nodule detection by (CAD) software.

Currently, several methods exist to suppress bone and other calcified structures in digital chest radiographs. One method is hardware-based, Dual Energy Subtraction (DES) radiography (GE Healthcare). Oda et al. (2009) determined that the use of DES radiography significantly improved the radiologists’ diagnostic performance in detecting ROI. Other studies found that hardware-based bone suppression (DES) removed the presence of bony structures in digital chest radiographs and significantly improved the sensitivity of CAD, which reduced the false-positive diagnosis rate (Balkman, Mehandru, DuPont, Novak, & Gilkeson, 2010; Li et al., 2011; Sacco-Parkas, Patak, Yuscel-Hutz, Rader, & Vock, 2010). Unfortunately, body fat attenuation of the body is more difficult to interpret the results of radiological examinations (Larson, Franzblau, Lewin, Goodman, & Antao, 2014; Rajapakse & Chang, 2014). Increased levels of obesity make diagnostic determination of physiological landmarks more difficult (Ambardar et al., 2009), but also make the results of other imaging procedures less accurate (Carboni, Sedati, & De Marco, 2013; Twaij et al., 2013). The purpose of this study was to compare the diagnostic effectiveness of CAD+DES bone suppression software combination to detect malignant pulmonary nodules when used on patients with differing levels of obesity as measured by BMI. As stated earlier, increased numbers of false positives (FP) and false negatives (FN) reduce the diagnostic efficacy and utility of CAD products in diagnostic radiology. The hypothesis of this study is that increasing levels of obesity alter the diagnostic efficacy and the number of ROI and FP marked by CAD.

METHODS

Institutional review board approval was obtained from University Hospitals Case Medical Center for this project. The approval for informed patient consent was waived and patient records were handled in compliance with Health Insurance Portability Accountability Act (HIPAA) regulations. All patient images and records were maintained on encrypted storage devices to maintain HIPAA compliance.

PATIENT SELECTION

Medical records and images from University Hospitals Case Medical Center were reviewed and sixty patients with either pulmonary nodules confirmed by 16 or 64 slice CT. In individuals with malignant nodules, the size and location were measured and marked on standard postero-anterior (PA) radiograph by an expert radiologist with 24 years of experience. Patient records were reviewed for height and weight, gender and age. Patients were divided into obesity groups by BMI and classified as: Normal (BMI=18.5-25), Overweight (BMI=25-30), Obese (BMI=30-40) and Morbidly Obese (BMI=40+). Underweight individuals (BMI < 18.5) were omitted from the analysis. Due to the small sample size, two groups were formed; normal individuals (18.5<BMI≤25) and overweight, obese and morbidly obese (OOMO, 25<BMI≤47).

SOFT TISSUE IMAGE AND CAD SOFTWARE ANALYSIS

DES radiography, one form of bone suppressed image generation, was performed on a Revolution XR/Definium™ digital radiography unit (General Electric Medical Systems). This radiography unit consisted of a 41 x 41 cm2 amorphous silicon based flat panel detector. DES radiography is performed using the acquisition of a low energy 60 kVp PA chest radiograph taken after a 150 ms delay, and a high energy 120 kVp radiograph. Subtracted and bone-enhanced images are also presented after post-processing of the high and low energy radiographs as depicted in Figure 1.

Figure 1: Dual Energy Subtraction Image Production Flowchart

Does BMI Affect Diagnostic Efficacy in Identification of Malignant Modules?

OnGuard™ Computer Aided Diagnostic (CAD) software was used to identify potential ROI that may be identified as malignant nodules. The stand-alone version of CAD software known as OnGuard™ (Riverain Technologies, Miamisburg, Ohio, USA) was utilized for this study as OnGuard, Version 5.2. Unlike previous versions, OnGuard™ Ver. 5.2 incorporated an additional bone suppression algorithm to better identify areas of interest prior to applying the CAD markings to the radiographs. The CAD component of the OnGuard™ CAD system identified ROI by imposing circular markings on the radiographs.

DISCUSSIONS

Definium™ digital radiography unit (General Electric Medical Systems). This radiography unit consisted of a 41 x 41 cm2 amorphous silicon based flat panel detector. DES radiography is performed using the acquisition of a low energy 60 kVp PA chest radiograph taken after a 150 ms delay, and a high energy 120 kVp radiograph. Subtracted and bone-enhanced images are also presented after post-processing of the high and low energy radiographs as depicted in Figure 1.
Examples of CAD markings on a bone suppressed DES image is shown in Figure 2. The circular markings were centered about a detection location that signified the identification of a probable malignant nodule. For identification of true positive detection and sensitivity, the known central point of the known nodule location must have been enclosed by the circular marking method of the CAD software and greater than 50% of the radiologist outlined nodule must have been also enclosed by the CAD mark. All other ROIs were determined to be false positives including those generated on CT proven negative cases. Figure 3 depicts true positive and false positive example markings on a bone suppressed DES image.

STRIALISITCAL ANALYSIS

SPSS Version 21 statistical software (IBM Corp, Armonk, NY) was used for statistical calculations. Correlation between several variables and ROI and FP frequency were evaluated by using the Spearman Rank Correlation test, chosen because of the non-normal distribution of ROI and FP. Test sensitivity and specificity were calculated using standard methods, Analysis of Variance (ANOVA), Chi-Square, the Z-test for Equality of Proportions and significance. P-values less than 0.05 were considered significant. To identify statistically significant differences between BMI groups, P-values less than 0.05 was considered significant.

RESULTS

Demographic and radiologic data was obtained on a total of 53 patients. Thirty patients had CT and pathology verified malignant pulmonary nodules and twenty-three were identified as malignant nodules free by CT. Overall, there were 24 females and 29 males. Sixteen females and seventeen males had malignant nodules and eight females and twelve males were in the non-malignant group. This distribution by gender was not significantly different by Chi-Square (p=0.75). The number of both ROI and FP did not differ by gender, (0.24<p<0.27). Patients with malignant nodules were significantly older than those that were malignant free (69.1 yr. vs 48.8 yr.; t=-20.4, p<0.001). However, when divided into Normal (n=26) and OOMO (n=27) groups, there was no significant difference in age (59.3 yr. vs 63.3 yr.; t=0.91, p=0.37).

For all patients, the diagnostic efficacy of CAD in the detection of malignant pulmonary nodules was: Sensitivity=81.8%, Specificity=60.0%. For Normal patients: Sensitivity=80.0%, Specificity=72.7%. For OOMO patients: Sensitivity=83.3% but Specificity was reduced to 44.4%. There was no significant difference between Normal and OOMO patients in the Sensitivity of CAD in detecting malignant nodules (80.0% vs 83.3%; p=0.94). The difference in Specificity between the Normal and OOMO patients approached significance (p=0.09). For either the BMI or OOMO group, there was no significant correlation between BMI and the number of false positive markings.

CONCLUSIONS

This pilot study did not find a statistically significant difference in the Specificity of malignant pulmonary nodule detection between the Normal and OOMO BMI groups. However, while there was no statistically significant difference in Sensitivity between the Normal and OOMO groups, a reduction in Specificity from 72.7% in the Normal group to 44.4% in the OOMO group is likely a clinically significant difference. The presence of obesity in a patient appears to obscure the ability of CAD to correctly identify the absence of malignant pulmonary nodules in OOMO patients, possibly increasing the number of false positive markings in this group. While the use of CAD in the detection of malignant pulmonary nodules in digital chest radiographs was designed to supplement the diagnostic capability of thoracic radiologists, decreased diagnostic efficacy in obese patients may limit the utility of this technology. Further, both the statistical tests for differences for Specificity between the OOMO and Normal BMI groups and significant rank correlation between the ROI and BMI for the normal group approached significance, suggesting that obesity may cause a statistically valid decrease in the diagnostic efficacy of CAD in patients with increased levels of obesity. The results of this study were limited by the small number of patients available during the study timeframe, particularly in the obese and morbidly obese BMI groups. A study with a larger number of patients, particularly in these two BMI groups may provide more insight and a more accurate view of this apparent discrepancy. Since obesity has already been found to affect the ability of radiologists to accurately identify physiological landmarks, interpret test results and utilize specific procedures in diagnostic radiology, the determination of whether or not the diagnostic efficacy of CAD is altered by increased levels of obesity in evaluating digital chest radiographs for malignant pulmonary nodules seems to be a pertinent and timely question that should be investigated further.
Using Flow Cytometry and Quantitative Real-Time PCR to Investigate the Role of IL-1 in T-Cell Proliferation and HIV-1 Reactivation

So Hee Moon

ABSTRACT

With the advent of antiretroviral therapy, suppressing the HIV-1 virus and stopping the progression of the disease are now possible. Even with long-term antiretroviral therapy, HIV reservoirs remain in individuals. These individuals experience an increase in inflammatory cytokines such as IL-6 and IL-1β that results in the proliferation of CD4 T-cells. In this study, we explored the relationship between inflammatory cytokine-induced proliferation and reactivation. To assess this relationship, we investigated the role of a specific inflammatory cytokine, IL-1β. It was concluded from our experiments that CD4 T-cells are able to proliferate in the presence of IL-1β. Although IL-1β may not induce overt reactivation of HIV-1, as shown in the flow cytometry data, further studies need to be conducted to see whether or not IL-1β propagates the reservoir.

INTRODUCTION

The single-stranded RNA virus human immunodeficiency virus-1 (HIV-1) presents a major public health crisis worldwide. Approximately 1.1 million people in the United States currently live with HIV, but only four out of five people realize that they are infected with the virus (Hall et al., 2008). The HIV-1 RNA and the reverse transcriptase enzyme, which synthesizes a complementary DNA strand is from this viral RNA, are contained within the nucleocapsid shell of the virus. This shell is encapsulated within a lipid bilayer that incorporates an integral membrane glycoprotein (gp41) and an associated glycoprotein (gp120). Associated glycoprotein molecules bind to CD4 molecules on the surface of helper T-cells. This interaction allows gp120 to insert its amino-terminal head into the host-cell membrane, causing the viral and T-cell membranes to fuse, which releases the viral core into the cytosol. Ultimately, the viral RNA can become DNA that is integrated into the host chromosome, which may kill the T-cell. The latent reservoir is a pool of cells that contain viral DNA but do not make active viruses (Berg et al., 2010). Therefore, HIV-1 results in decreased levels of the CD4 T-cell population. CD4 T-cells help individuals fight infections. Decrease in CD4 T-cells due to HIV is associated with chronic inflammation and acquired immunodeficiency syndrome (AIDS).
Due to its high mutation rate, the error-prone replication of HIV presents an ever-changing array of coat proteins, making it difficult to develop an effective vaccine. HIV-infected individuals are commonly treated with highly active antiretroviral therapy (ART) that utilizes a combination of several antiretroviral drugs. With ART, individuals typically experience an increase in CD4 T-cell counts and an improvement in immune function. ART can reduce plasma HIV-1 RNA levels below the detection threshold of clinical assays, which is usually 50 copies/mL (Doyle et al., 2012).

Due to this decrease in RNA level, previous studies have predicted that 2.3 to 3.1 years of ART could potentially cure HIV-1 infection (Perelson et al., 1997).

However, recent studies have shown that complete eradication of HIV is impossible even after two to three years of ART. For example, the “Mississippi baby,” whose mother was HIV-1 positive, started ART within hours of birth. Although the child had undetectable levels of viral matter after a prolonged withdrawal from treatment and was thought to be cured of HIV, her virus still demonstrated reactivation after treatment was stopped (Stover et al., 2014). Similarly, although viral loads may appear low due to successful ART, patients experience an increase in inflammatory cytokines such as IL-6 and IL-1β. This, in turn, results in the proliferation of CD4 T-cells, a major site of latent virus reservoir (Shive et al., 2014). When HIV reactivates upon removal of treatment, CD4 T-cells proliferate and produce more viral proteins. Therefore, HIV-1-infected individuals currently require lifelong ART to prevent a small but longstanding HIV latent reservoir from infecting more cells (Bosque et al., 2011).

The aim of this study is to assess whether proliferation induced by IL-1β is associated with reactivation. IL-1β, or a cytokine that induces various inflammatory and immune responses. Compared to uninfected subjects, HIV-1-infected patients express increased levels of IL-1β within all anatomical sites of the lymph nodes, especially in medullary cords, sinuses, and the T-cell zone (Shive et al., 2014). Patients who receive ART also express some level of IL-1β (Shive et al., 2014). To assess the relationship between IL-1β-induced proliferation and reactivation, we used flow cytometry and real-time polymerase chain reaction (PCR). Flow cytometry was used to measure the relative percentages of viral reactivation and proliferation, and to distinguish cells that divided after stimulation with IL-1β from those that did not. A Carboxyfluorescein succinimidyl ester (CFSE) dilution was performed to assess the rate of proliferation of cells stimulated with IL-1β. In addition, real-time PCR was used to quantify viral RNA levels in the supernatant that was released from the cells.

**MATERIALS AND METHODS**

**Ethics Statement**

All participants in this study willingly provided written informed consent and fully understood the purpose and methods of this project. Patient characteristics are shown in Table 1. Two samples of blood were collected from three viremic patients. The blood samples were collected from three viremic patients. Blood samples from three viremic patients were collected.

**Peripheral Blood Mononuclear Cell (PBMC) Purification from Whole Blood**

Blood samples from three viremic patients were collected. Patient characteristics are shown in Table 1. Two samples of blood were used to quantitate viral RNA levels in the supernatant of untreated HIV-1-infected patients express increased levels of IL-1β within all anatomical sites of the lymph nodes.

The aim of this study is to assess whether proliferation induced by IL-1β is associated with reactivation. IL-1β, or a cytokine that induces various inflammatory and immune responses. Compared to uninfected subjects, HIV-1-infected patients express increased levels of IL-1β within all anatomical sites of the lymph nodes, especially in medullary cords, sinuses, and the T-cell zone (Shive et al., 2014). Patients who receive ART also express some level of IL-1β (Shive et al., 2014). To assess the relationship between IL-1β-induced proliferation and reactivation, we used flow cytometry and real-time polymerase chain reaction (PCR). Flow cytometry was used to measure the relative percentages of viral reactivation and proliferation, and to distinguish cells that divided after stimulation with IL-1β from those that did not. A Carboxyfluorescein succinimidyl ester (CFSE) dilution was performed to assess the rate of proliferation of cells stimulated with IL-1β. In addition, real-time PCR was used to quantify viral RNA levels in the supernatant that was released from the cells.

**Table 1. Clinical characteristics of 3 Human Immunodeficiency Virus (HIV)-Infected Subjects Examined in this Study. ART indicates antiretroviral therapy. All three subjects are HIV-infected, viremic patients.**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>ART Status</th>
<th>Gender</th>
<th>Year Born</th>
<th>Plasma HIV RNA (Copies/mL)</th>
<th>CD4 T-Cell count (Cells/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5210</td>
<td>Treated in the past</td>
<td>Male</td>
<td>1976</td>
<td>19601</td>
<td>574</td>
</tr>
<tr>
<td>5240</td>
<td>Untreated</td>
<td>Male</td>
<td>1991</td>
<td>11552</td>
<td>637</td>
</tr>
<tr>
<td>5224</td>
<td>Treated in the past</td>
<td>Male</td>
<td>1993</td>
<td>9618</td>
<td>770</td>
</tr>
</tbody>
</table>

**Harvest and Staining for Flow Cytometry**

After 7 or 12 days, the plate was removed from the incubator. The bottom of each well was scratched to dislodge adherent cells and then placed into a flow tube. The flow tube was spun for 3 minutes, and supernatant was saved for later use (i.e., real-time PCR). After spinning, PBS and Live/Dead (Yellow: Molecular Probes) dye were added into each tube and the tubes were incubated in the dark for 20 minutes at room temperature. T-cell phenotypes were quantitated using several fluorochrome-conjugated monoclonal antibodies CD4-BV421 (Clone: RPA-T4; BD Biosciences), CD4-PerCP-Cy5.5 (Clone: RPA-T8; BD Biosciences), and CD8-PerCP (Clone: RPA-T8; BD Biosciences), and the mixture was stained with antibody staining cocktail for 20 minutes at room temperature in the dark. Afterwards, the cells were spun, washed, and fixed in PBS-paraformaldehyde solution. To detect intracellular p24, the cells were washed and permeabilized with a saponin-based buffer (BD Biosciences) and incubated with p24-PE antibody (Clone: KC57-RD1, Coulter Clone) for 40 minutes on ice. Cells were acquired on an LSR-II flow cytometer (BD Biosciences) using BD FACS Diva software (version 6.2, BD Biosciences), and analyzed using FlowJo software (version 8.8.7, TreeStar).

**RNA Isolation**

A sample of supernatant from PBMCs stimulated with IL-1β or PHA was mixed with buffer AVL and a carrier RNA mix from RNeasy® Mini Kit (Qiagen). The mixture was incubated at room temperature, and 100% ethanol was added. The mixture was then spun into a spin column from the mini kit, and spun down at 8000 rpm (6800g) for one minute. The flow-through was discarded, and another sample of the mixture was spun down. Then buffer AW1 with ethanol was added, spun down at 8000 rpm for one minute, and the flow-through was discarded. Buffer AW2 was added, the column was again spun down at 14000 rpm (28000g) for 5 minutes, and the flow-through was discarded. The spin column was placed into a Eppendorf tube, followed by the addition of buffer AVE. The tube was incubated for at room temperature. Finally, the tube was spun down at 8000 rpm for one minute and the elution was stored for complementary DNA (cDNA) synthesis.

**cDNA Synthesis**

cDNA was synthesized from reverse transcriptase with High-Capacity RNA-to-cDNA kit (Applied Biosystems, Grand Island, NY). A small sample of RNA from Qiagen kit RNA Isolation was added to HIV-1 reverse Gag primer (5’GTCCTTGGACTTTGCTAATCTC-3’). The mixture was incubated in a thermal cycler. A mixture containing first strand buffer, 0.1M DTT, 10mM dNTPs, and RNase-free water was added. The new mixture was once again incubated in the thermal cycler. Then, a mixture containing Moloney Murine Leukemia Virus Reverse Transcriptase (M-MuLV RT) and RNase-free water was added, followed by prolonged incubation in the thermal cycler.

**RNA Measurement by Real-Time Quantitative Polymerase Chain Reaction (PCR)**

A sample of cDNA was amplified using the StepOnePlus real-time quantitative PCR (Applied Biosystems). The cDNA was mixed with TaqManFast Master Mix, forward primer (5’-CCGAGCTTGCACCGCTGGGAGCTC-3’), reverse primer (5’-GCTTGGGGCGCCGCACTGCG-3’), and RNase-free water. The mixture was incubated in the thermal cycler.

Pre-amplified products were subjected to a nested real-time PCR. In a new PCR plate, a sample of the mixture from the previous step was added in duplicates to a mixture containing TaqManFast Master Mix, forward primer (5’-TTAAAGCTTACCTAATGG-3’), reverse primer (5’-GGTGGCCGACCATGCTA-3’), and U5 probe (5’-GTGGCCGACCATGCTA-3’), ultraspecific primer (5’-FAM-CGAGCTTACCTAATGGGAGCCTC-3’), reverse primer (5’-GCTTGGGGCGCCGCACTGCG-3’), and RNase-free water. The mixture was incubated in the thermal cycler.

Due to its high mutation rate, the error-prone replication of HIV presents an ever-changing array of coat proteins, making it difficult to develop an effective vaccine. HIV-infected individuals are commonly treated with highly active antiretroviral therapy (ART) that utilizes a combination of several antiretroviral drugs. With ART, individuals typically experience an increase in CD4 T-cell counts and an improvement in immune function. ART can reduce plasma HIV-1 RNA levels below the detection threshold of clinical assays, which is usually 50 copies/mL (Doyle et al., 2012). Due to this decrease in RNA level, previous studies have predicted that 2.3 to 3.1 years of ART could potentially cure HIV-1 infection (Perelson et al., 1997).
**RESULTS**

**Gating Strategies for Flow Cytometry Analysis**

As shown in Figure 1, cells were first gated for singlets to exclude cell aggregates (forward scatter area vs. forward scatter height, not shown), and then lymphocytes (side scatter vs. forward scatter shown in Figure 1a). The lymphocytes gate was further analyzed for its uptake of the Live/Dead-Yellow viability dye in order to determine live versus dead cells and their expression of CD3 (Live/Dead Yellow vs. CD3 shown in Figure 1b). The live, healthy T-cell population (CD3 positive) was gated and dead cells were excluded. T-cells that lacked CD8 expression were used for further analysis (Figure 1).

**Comparing HS and FBS**

Previous studies suggested that in vitro studies about HIV-1 are usually performed in human cell cultures supplemented with FBS due to efficient proliferation (Perdomo et al., 2012). It was expected that IL-1β would induce better proliferation in FBS than in HS. It was also expected that this would allow a second level of analysis to determine the relationship between proliferation and reactivation. When PBMCs treated with polyhydroxyalkanoates (PHA) were supplemented with HS, however, more cells reactivated, as shown in Figure 2. In addition, both of the cells that proliferated and those that did not reactivated. The data suggests proliferation and reactivation are uncoupled from each other. It also suggests there is an additional factor with human serum that induces reactivation. The assay was not particularly sensitive because there was not a significant release of virus when PBMCs were left in the presence of IL-1β, as measured by Gag protein expression.

**Infiammatory cytokine IL-1β induces CD4 T-Cell proliferation**

It was observed that cells stimulated by the inflammatory cytokine IL-1β proliferated. Three PBMC samples were prepared from two viremic patients who received no ART and one viremic patient who had received ART in the past but was no longer on therapy (Table 1). Viremic patients were used for this study since the measurement of reactivating virus was expected to be more feasible given their high viral loads. To track cell division, the cells were labeled with carboxyfluorescein succinimidyl ester (CFSE) dye and stimulated with IL-1β or PHA for 7 days. CFSE dye allows for a direct measurement of cells undergoing division, since each cellular division dilutes the dye. As shown in Figure 1, 1L-1β induced cell division in both FBS and in HS. PHA induced the highest level of cell division, and media alone induced the lowest level of cell division. In all three cases, cells divided at a higher rate when they were subjected to FBS than HS.

**DISCUSSION**

In this study, flow cytometry and quantitative real-time PCR were used to address how inflammatory cytokine IL-1β is associated with HIV latency. Measuring CFSE dilution by flow cytometry allowed direct measurement of cell proliferation stimulated with IL-1β. As the two acetate groups in CFSE fluorescence allowed the dye to readily cross the plasma membrane of the cell during division, of viral RNA in the supernatants. Although IL-1β did not induce viral reactivation as measured by flow cytometry, viral RNA levels increased in Real-time PCR to about five-fold in the presence of FBS and eight-fold in the presence of HS (Figure 4e). The results indicate that IL-1β can potentially lead to viral expression in persistently infected cells, even in the absence of detectable Gag expression. As expected, PHA in the presence of HS resulted in the greatest amount of viral RNA. Interestingly, when viral RNA levels were measured in copies/mL, a substantial amount of viral RNA was detected even in the negative control (Figure 4c). The presence of the viral RNA could be due to the amplification steps in which a small amount of RNA was amplified during the real-time PCR, or because viremic samples were used in this study. Samples from HIV-positive individuals who are not viremic may have lower baseline HIV RNA levels. In addition, the number of RNA copies was generally lower after 12 days of treatment, as shown in Figure 4c. Other cells may have stopped the virus, cells themselves may have died so that fewer cells were replicating the virus, or cells that reactivated may have become transient.
PCR allows the virus to be detected in a small target sequence. A single-stranded DNA probe, which contains a fluorescent molecule and a quencher, is hybridized to the part of the DNA sequence synthesized between the two primers. By amplifying the target sequence, the quencher allows the fluorescent molecule to emit detectable light when the fluorescent molecule is released from its neighboring quencher. Therefore, in each PCR cycle, the amount of emitted light doubles as the fluorescent molecule is released from the quencher. The amount of viral RNA is then determined by a reference to the rounds of PCR in which the amount of fluorescence first crosses the threshold of detection, calculated from the standard curves shown in Figure 4a.

The flow cytometry data indicates that IL-1β induces little viral reactivation, although it induces proliferation. However, in real-time PCR, viral RNA levels increased in the presence of IL-1β when the sequences were amplified. From these observations, it can be deduced that only a few T-cells produce virus make up a lot of virus to maintain the latent CD4 T-cell reservoir. Although IL-1β does not induce overt reactivation of HIV as shown in this study, this does not mean that IL-1β may not contribute to the maintenance of the reservoir. Over time, few cells may produce the virus after IL-1β treatment in the population that proliferates, or the population that does not. Therefore, further studies need to be conducted to assess the direct mechanism that addresses how the latent viral reservoir is maintained over time in HIV-1 infected patients.

**REFERENCES**


ABSTRACT

To maintain sodium (Na+) homeostasis in a hypotonic environment, freshwater teleosts must constantly absorb Na+ through their gills. Teleosts in temperate climates have the extra challenge of living in an environment in which ambient temperatures range from 0-30°C. It was hypothesized that 1. Na+ absorption through the gills occurs via a protein homologous to mammalian Na+/H+ exchanger (NHE), 2. Na+ is exchanged for NH4+—the nitrogenuous waste product of the fish—rather than H+, and 3. gill proteins from 5°C winter-acclimated fish (WA) would be more active than those from 20°C Summer-acclimated fish (SA). To test this, the genome and transcriptome of SA fathead minnows (Pimephales promelas) were sequenced and assembled. RNA and DNA from SA were isolated using the Qiagen RNeasy Kit by manufacturer’s protocol (Cat. No. 74134, Qiagen, Hilden, Germany). Two libraries were created for each temperature range using an Illumina HiSeq 2500 (Illumina, San Diego, CA). Sequencing was done in two lanes, one for each experiment.

INTRODUCTION

There are many models for how freshwater (FW) teleosts maintain Na+ homeostasis in hypotonic environments. August Krogh was the first to propose a model for Na+ uptake. He discovered that Na+ and Cl− absorption were independent processes and that Na+ was exchanged for NH4+. Later tests by Avella and Borrancin (1989) showed that Na+ was more likely exchanged for protons rather than ammonia. 

Recent research has shown there are three major models for Na+ uptake in FW fish: electrically coupled exchange using the epithelial Na+ channel (ENaC) linked to an H+−ATPase, uptake via Na+/H+ exchanger (NHE), and Na+ and Cl− co-transport (NCC) (Kumai & Perry, 2012). However, these models all have certain aspects that make them incomplete. For example, while the ENaC model works thermodynamically, there has been no evidence of ENaC or its homologues in sequenced FW fish genomes (Dymowska et. al, 2012). Genomic studies of the rainbow trout have shown the presence of NHE, but since it is driven by the concentration gradients of Na+ and H+, it should not be able to function in FW environments since extracellular Na+ is lower than intracellular Na+/Parks et al. (2008). One suggested way of overcoming the thermodynamics of NHE is through the use of ammonia transporters (Rh factors). Natawa and associates (2007) have proposed that Rh factor transporters protein transport NH3 out of the cell where it combines with H+ to form NH4+, causing an increase in local pH outside the cell making it favorable for Na+ transport via NHE. This model depends heavily on the creation of a microenvironment that is unbuffered, but given the anatomy of the gill, and the high flow rate of water across the filaments, this unbuffered layer is unlikely to exist. The last model, NCC, has only recently been identified in FW teleosts (Hirok et al. 2008), but N+ absorption via this transporter is also thermodynamically unfavorable given the extracellular and intracellular concentrations of Na+ and Cl− (Evans, 2011). 

It was proposed that N+ absorption occurs by Krogh’s original model in which extracellular Na+ is exchanged for intracellular NH4+ and that NHE is the protein that facilitates this exchange.

In addition Na+ absorption, FW teleosts in temperate climates must be able to maintain enzyme function from 0−30°C. Since enzyme function falls with decreasing temperatures, such a large range poses a challenge for epithelial transport proteins maintaining Na+ homeostasis. Research by Packer & Garvin (1998) has shown that Na+/K+ ATPase (NKA) activity is higher in cold acclimated teleosts compared to warm acclimated teleosts when assayed at the same temperature. NKA moves Na+ from the intracellular milieu to the blood, thus generating the concentration gradient needed for Na+ re-absorption. Possible causes for the change in activity include changes in protein expression, membrane lipids, or transport protein subunits.

The Rosy Red fathead minnow (Pimephales promelas) was chosen for this study because of its use in ecotoxicology, commercial importance, and ability to tolerate environmental conditions under various temperatures, pH, and alkalinity. A member of the Cyprinidae family, the fathead minnow is broadly distributed across North America and is the model organism for aquatic toxicology studies and the Rosy Red strain is sold in pet stores as aquarium fish (Ankley & Villedeneuve, 2006).

It was hypothesized that 1. Na+ absorption through the gills occurs via a protein homologous to mammalian Na/H+ exchanger (NHE), 2. Na+ is exchanged for NH4+, the nitrogenuous waste product of the fish, rather than H+, and 3. Gill proteins from 5°C winter-acclimated fish will have higher activity than those from 20°C summer-acclimated fish (WA). This hypothesis was tested by sequencing the transcriptome of a SA Rosy Red and measuring the activity of transporters potentially involved in Na+ re-absorption using fluorescence tagging.

MATERIALS AND METHODS

RNA Preparation

Rosy Red Fathead minnows were acclimated to 22°C prior to RNA extraction. Fish were injection with heparin then anesthetized in MS-222 Tricane solution and dissected on ice. The opercula were removed and the ventral adenos opened from anal fins to gills. Tissue and bone were removed to expose the ventricle. A 30G needle was inserted into the corus arteriosus, then pushed into auria and tied in with 8-0 suture to prevent back flow, and the gills were flushed with 6ml of physiological saline and heparin. Gill filament RNA was extracted using the Qiagen Rneasy® Plus Mini Kit by manufacturer’s protocol (Cat. No. 74134, Qia-gen, Hilden, Germany). Two samples were made, one from the right gill basket and the other from the left gill basket. RNA quality and content was determined using a Nanodrop Spectrophotometer, RNA samples were kept at -80°C until sequenced.

RNA Sequencing, assembly, and annotation

RNA sequencing and library preparation was performed by the Case Western Reserve University Genome Sequcing Core using an Illumina HiSeq 2500 (Illumina, San Diego, CA, USA). Samples of 140 µg and 7.6 µg of RNA were used to construct two CDNA libraries using an Illumina TrueSeq Stranded mRNA Sample Prep Kit (Illumina, San Diego, CA). Sequencing was done in two lanes, one for each
sucrose solution. Both were run through a 26.5G needle 20 times to allow the new solutions to be taken up by the vesicles. The solution was then spun at 50,000xG for 60 minutes to collect the vesicles. The pellets were finally suspended in 1.2 mL sucrose solution.

Table 2. Summary of transcriptome analysis. Over 42,000 unique genes were found, and the high mean length indicates a transcriptome of high quality.

| Total Reads | 470,812,874 |
| Conversion | 700V |
| Excitation Slit | 5mm |
| PMT Voltage | 700V |

While the entire transcriptome was annotated, transporters related to Na+ uptake were detected: namely, transcripts corresponding to NHE, NCC, Na/HCO3 and Na/K ATPase (NKA). No transcripts related to ENaC or the Na/K/Cl cotransporter (NKCC) were detected. Initial query showed 14 different Rh factor proteins present in the transcriptome though due to false positives this number may be lower (Figure 1). From the transporters found in the transcriptome, a working model was developed for sodium entry. In this model, NHI is taken into the cell via Rh factor proteins where it combines with H+ from carbonic acid in the cell making NH4+. The NH4+ is used in place of H+ in NHE, thus allowing Na+ uptake into the cell. NHI is then transported into the blood via NKA and the Enzyme activity of gill membrane vesicles containing the sodium-sensitive fluorescent dye, Sodium Green, was measured. Using the initial rates from each concentration, a Micheal-Menien plot was created where $V_{max}=141$ and $K_{1/2} = \pm 7.5$. These indicate that rates in fluorescence were due to carrier-mediated transport of Na+ into the vesicles (Figure 3). These data suggest the existence of Na+/H+ exchanger, Na+/HCO3-, Na+/Cl- co-transport, Na+/K+ ATPase, and NH3 transporters as these were identified in the gill transcriptomes but neither the ENAC nor NKCC2 were present in the transcriptomes. Regardless, Na+ influx kinet- ics remained consistent with NHE as a mechanism of entry. With these data, it is possible to construct a novel working model for how Na+ is absorbed through the gill epithelium. Future studies should focus on differential expression between SA and WA gill transcriptomes to identify differences at the mRNA level. These differences can then be linked to changes in function using fluorescent tagging.

**RESULTS & DISCUSSION**

The results of sequencing the gill RNA of P. promelas using an Illumina HiSeq 2500 resulted in high quality raw reads, trimming and assembly, as determined by the large mean length of each transcript (Table 2).

**Fluorescence**

Each sample was placed into a 3 mL cuvette with stirring. Over the course of 60 seconds, volumes of 150 mM NaCl were added corresponding to final Na+ concentrations of 2, 4, 6, 8, 16, and 32 mM and the change in fluorescence measured.

**REFERENCES**


Krogh A, 1874-1949 (1939) Osmotic regulation in aquatic animals, En- gland; United Kingdom.


ABSTRACT

Purpose
There are more than 6,000 different genetic diseases manifested in 1/200 live births. These children are often part of a family with siblings. The purpose of the study was to learn through interviews the lived experience and needs among college students with siblings who have a genetic disease such as Cerebral Palsy, Muscular Dystrophy, Sickle Cell Anemia, Cystic Fibrosis, Down syndrome, Trisomy 13, Schizophrenia and Bipolar Disorder that requires multiple hospitalizations. The aims of the study were to: 1) explore the lived experience of the college-aged student in a family unit that is living with a genetic disease process, 2) learn how the university may support these students, and 3) identify nursing interventions that would benefit all-aged siblings of patients with a genetic disease.

INTRODUCTION

It has been noted that there are more than 6,000 different genetic diseases, manifested in 1/200 live births (Stoppler, 2014). Birth defects often associated with genetic disease affect one in every 33 infants born in the United States every year (Centers for Disease Control and Prevention, 2014). A child with genetic disease often requires many planned and unplanned hospitalizations, and the family unit along with that sibling may experience unexpected changes in routines, priorities, and increased demands on parental resources. The purpose of this qualitative study was to learn the lived experience and needs among college students with siblings who have a genetic disease such as Cerebral Palsy, Muscular Dystrophy, Sickle Cell Anemia, Cystic Fibrosis, Down syndrome, Trisomy 13, Schizophrenia and Bipolar Disorder that requires multiple hospitalizations. The aims of the study were to: 1) explore the lived experience of the college-aged student in a family unit that is living with a genetic disease process, 2) learn how the university may support these students, and 3) identify nursing interventions that would benefit all-aged siblings of patients with a genetic disease.

REVIEW OF THE RECENT LITERATURE

Orsmond and Selzer (2009) have reported that examination of the status and needs of those who have siblings with a genetic disease has been limited. Those published largely focus on younger sibling children up to 18 years of age. There are numerous gaps and discrepancies in quality that currently plague sibling research, attributed to inconsistencies in methodology and lack of rigorous sampling (Macks & Reeve, 2007). Often seen in sibling research are survey instruments utilized to assess psychological functioning, family functioning, depression, family burden, child behavior, and quality of life (Gold, et al., 2008; Read, et al., 2008; Read, et al., 2011). Researchers also examined the healthy child’s knowledge of their siblings’ disease, such as sickle-cell disease, and findings indicated that such knowledge may be a critical factor related to their behavior (Gold, Treadwell, Weissman, & Vichinsky, 2011; Lobato & Kao, 2002).

Clinical Implications

It is acknowledged that sample size was low and results may be anecdotal. However, there were repeating comments and themes identified. Universities are in a position to nurture these students towards adulthood. Pediatric nurses need to recognize the needs of siblings of patients and deliver family-based holistic care. Future research calls for a larger, more diverse sample.

Results

Three female, Caucasian students participated. Three themes were identified: defining a new normal, caregiver role strain, and experiencing a crippling social life. Participants made suggestions for supportive nursing and university interventions.

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INTERVIEWS WITH STUDENTS

METHODS

This is a cross-sectional qualitative pilot study with a phenomenological perspective. Phenomenology is a method of inquiry based on the premise that reality is what a person perceives or understands (Burns & Grove, 2009). Phenomenology is about the lived experience.

The conceptual framework included the developmental theories of Erikson and Sullivan. Erikson (1993) speaks of stages that need to be resolved in each age group to move successfully toward adulthood. The university student straddles two stages. Erik Erikson theorized that the university student would be leaving the stage of identity versus role confusion – where there is a questioning of self and where the student is going in life – and entering the stage of intimacy versus isolation – the first stage of adult development – where friendships and dating are important. Sullivan's Interpersonal Theory includes dynamics of self-system that protects one from anxiety and maintains interpersonal security (Stern & Marchesani, 2004).

For the college-aged student, it is the stage of forming lasting, intimate relationships that are crucial for the university student to develop. Relationships have the power to transform an immature preadolescent into a psychologically healthy adult individual (Evans, 1996).

Sample and setting

The setting was a university campus with an enrollment of approximately 3,700 students. The University is a liberal arts college that draws on the Lutheran principle of free inquiry. Students of the University were the target sample. Inclusion criteria included: age 18 to 25 years old, a University student who lived with that sibling for a least five years, been able to participate in a focus group conducted in English, and signed written consent forms. The focus group will be audio-recorded. All responses are protected by pseudonym names taken by the study participants and the wearing of pseudonym badges. Tent place cards with the fake name were made and placed in front of the participant for "identification." The only rule of the group was to interrupt one another and to not know that the forum was an open, trusting, non-threatening place where no judgments were made. A flip chart was used to visually record comments of the group, and reviewed with participants at the conclusion of the session. The qualitative session was one hour in duration and a $10 gift card was given as compensation for participation time.

Procedure

This study was approved in expedited review by the university Institutional Review Board. Recruitment flyers approved by the Student and Community Engagement Office were posted on bulletin boards in academic buildings and resident halls recruiting candidates for the study. E-mails were also sent out to students and faculty with the flyer attached.

Interested students were asked to contact an electronic mail account that was created exclusively for the study's purpose. In response to the e-mail inquiry of interest, a calendar was sent to establish a mutually convenient time for the interviews. Training was held prior to in conduct of the study. Initially, the study was designed to conduct a focus group, but limited student responses lead to the need for modification to conduct group and individual interviews.

Upon entrance into the study room the research team greeted the students. The study was explained and the potential participants were given time to ask questions. The consent form, the university Human Dignity Policy (that addresses respect for others and intolerance for bullying and harassment), and demographic form (student age, gender, race, ethnicity, birth order, and sibling's gender, age, diagnosis, number of hospitalizations, medications or therapies needed by the sibling, number of children in the family, and marital status of the parents) was e-mailed out in advance so that student participants had time to carefully read it over. The prospective study participants were given an opportunity to sign a consent form that acknowledges their voluntary participation and notes that the focus group will be audio-recorded. All identities were protected by pseudonym names taken by the study participants and the wearing of pseudonym badges. Tent place cards with the fake name were made and placed in front of the participant for "identification." The only rule of the group interview was to interrupt one another and to know that the forum was an open, trusting, non-threatening place where no judgments were made. A flip chart was used to visually record comments of the group, and reviewed with participants at the conclusion of the session. The qualitative session was one hour in duration and a $10 gift card was given as compensation for participation time.

Questions were asked of participants that included inquiry into their perceptions of family life such as: Share with us what it was like at home when your sibling was hospitalized? And how did your family talk about the genetic disease of your sibling? Questions were presented that sought insight into their experiences in the hospital setting when their sibling was admitted for care. Tell us a story about when you visited your sibling in the hospital. What, especially the nursing staff, could they have done to make you feel better? The concluding questions sought information on student support needs the campus community may need to consider. How do you think your sibling's disease or syndrome has impacted your personal growth in regard to development/maturity/independence/strategies for facing adversity?

RESULTS

Sample

All participants were Caucasian, non-Hispanic females. Two students were 22 and one was 20. There were two seniors and one freshman student. Their siblings with genetic diseases were: male with Arrhythmogenic Right Ventricular Dysplasia (a congenital heart disease), female with autoimmune Rheumatoid Arthritis, and male with Down's Syndrome. All students stated that they participate in home therapies such as physical therapy, occupational therapy, speech therapy, and act as a home health aide when outside assistants are not available. All university students shared stories of their sibling having multiple and unexpected hospital admissions. Two students had divorced parents. The hospitals frequented by the siblings ranged from 25 minutes to two and one-half hours away. A focus group style methodology was used for two participants. The third participant was unable to attend the session due to a conflicting academic schedule and asked to be interviewed. The same questions were used and the study was conducted in the same manner as possible.

A New Normal

Participant A said, “...now it’s like I feel like I don’t have a normal life, but it is normal to me just because I’m used to it.” Participant B expressed acceptance of her life’s situation, “Everyone’s normal is something different, going back would be weird.” Participant C whose brother had Down’s syndrome said, “Kids would ask me what was wrong with him [my brother]; I’d say nothing is wrong with him.”

Caregiver Role Strain

Participants talked about the conflict of being an adolescent and adult and the unique roles these siblings experienced and maintained in their families. One participant shared a story about participating in various therapy sessions as if he or she was the client. It was like I had to be his older sister [instead of the reality of the situation being the younger sibling]. “We are partners in crime, my brother and me. I went through physical therapy and speech therapy too to make it fun and easier for him, otherwise he wouldn’t do it.” Another participant expressed resolution about her personal future, “What can I do? and I can’t really do anything about it.” She continued...I am going to be the one to take care of her [when the sibling gets older] ‘cause I don’t know who else would be there for her.” In a matter-of-fact manner the third participant replied to a comment, “Yeah, I did [had to grow up early].” And the other two agreed.

DISCUSSIONS

Audio recording of dialogue was professionally transcribed verbatim, a person unknown to group members. The “long table approach” following the methodology of Morgan (1998) and Krueger (1998) and no computer software was used. In this process, the transcript was cut apart; common occurring phrases were put together and arranged into different categories found through the study. Themes were then identified from the categories. The use of a flip chart, field notes, debriefing, and data reconstruction also assisted in the identifications of themes, findings and conclusions.

Phenomenology is about the lived experience. Phenomenology is a phenomenological perspective. Phenomenology is a cross-sectional qualitative pilot study with a phenomenological perspective. Phenomenology is a method of inquiry based on the premise that reality is what a person perceives or understands (Burns & Grove, 2009). Phenomenology is about the lived experience.
Crippling university social life

The three participants all shared stories about the impact on their college personal life. The first student said, “I had exactly 2½ friends my freshman year at [university]. It was crippling socially. Like I mean gone every weekend. Gone social life.” The second student talked about her returning home to assist in care giving to respite her parent. “I go home every single weekend. I haven’t stayed one weekend this year.” The third participant talked about sleep disturbance when her sibling telephoned. “Sometimes by brother calls me at 2 AM to say, ‘just come home’, and, ‘why can’t I be in college.’”

Participants’ suggestions for nursing and university implications

To conclude the sessions participants were asked or suggestion on how nurses and universities could help them. They all agreed that acknowledgement of the well-siblings’ presence was important. They felt that nurses ignored them when they were visiting. “It’s like I exist too. I know that I’m here to support my sister, but I exist too, kind of thing.” The second student said, “I don’t remember any of the nursing staff ever explaining anything really to me. They kind of left that up to my parents.” The third participant summed up the group’s thoughts by saying, “It just doesn’t affect the siblings [child with genetic disease], but everyone...”

The participants were then asked what suggestions they had for universities to help in the well-siblings’ role in academic and university life. They offered three suggestions. The first was to establish a university support group. The purpose of the support group would enable them to “just sit down and talk.” They continued, “Yeah, [the support group] will enable them to ‘just sit down and talk’.” In addition, at the close of the interviews participants agreed they felt more confident to discuss their family circumstances with faculty advisors. Participants felt that holistic family-based care should include siblings in the delivery of nursing interventions. The two main opinions expressed by the participants were the nurses needed to increase communication and acknowledge the siblings’ presence (Box 1). Nurses also need to remember that there are multiple resources to utilize, such as child life, pastoral care, social work, or psychology.

**Challenges of the study**

It is acknowledged that the sample size was low and results may be anecdotal. However, even with a small sample size there was repeating comments and themes. While working with the Student and Community and Engagement Office in regards to distributing the flyers on campus, there was a break in communication and the flyers did not get posted until three weeks after the anticipated date, and another week was lost due to spring break. Attempting to recover lost time, we obtained permission to send a general email to the student body and faculty, and again posted flyers, but the end of the academic semester was approaching. The student researcher knew of other university students who may be interested. The inclusion criteria of the study, but they did not come forth. A second challenge was scheduling conflicts of the participants.

**CONCLUSION**

College-students did not want to use their siblings genetic disease as an excuse, but would appreciate some flexibility in due dates of assignments when family crises arose. They did agree, however, that speaking with advisors to potentially make deadline extensions would decrease schoolwork-associated anxiety. Participants suggested a “sibs” weekend that would enable visits by their siblings with genetic diseases. Something that was noteworthy was that, by the engaging discussion of the participants it was shown that a support group would be therapeutic as they shared a common bond. They also expressed conflict regarding getting tested for the genetically linked disease of their sibling. In addition, at the close of the interviews participants agreed they felt more confident to discuss their family circumstances with faculty advisors.

**REFERENCES**


Case Study


The Human Rights Impacts of VAWA 2013: A True Victory for Native American Women?

INTRODUCTION

The level of gender violence against native women in the United States has reached epidemic proportions. Furthermore, the vast majority of Native American gender violence victims are abused at the hands of non-native men. Native American tribes are considered to be “domestic dependent” of the United States, meaning that they have the inherent authority to govern themselves and also maintain U.S. citizenship rights. This system creates multiple overlapping governing systems on tribal reservations, as illustrated by determining jurisdiction over gender violence crimes. Tribal courts do not have the power to persecute non-native persons, and federal prosecutors, who do have jurisdiction, have declined approximately two-thirds of cases involving violence against indigenous women. James Anaya, the United Nations Special Rapporteur on the Rights of Indigenous Peoples, also expressed concern about the prevalence of gender violence on Native American reservations. Following his visit to the United States in 2012, he reported that numerous cases of violence against native women are committed by non-native individuals, many of whom are not subject to indigenous prosecutorial authority because of their non-native status. He asserts that “Congress should act promptly to pass key reforms to the Violence Against Women Act that bolster indigenous tribes’ ability to prosecute cases involving violence against indigenous women.”

Consequently, Native Americans have reached out to the international human rights community for support in gaining more legal protection for the victims of gender violence. Independent international experts and human rights organizations have repeatedly called on the United States to take action and increase legal protection for Native American women. Amnesty International claims that “In failing to protect Indigenous women from sexual violence, the US is violating these women’s human rights.” The human rights organization is calling on the United States government to take necessary steps to end sexual violence against Native American women. James Anaya, the United Nations Special Rapporteur on the Rights of Indigenous Peoples, also expressed concern about the prevalence of gender violence on Native American reservations. Following his visit to the United States in 2012, he reported that numerous cases of violence against native women are committed by non-native individuals, many of whom are not subject to indigenous prosecutorial authority because of their non-native status. He asserts that “Congress should act promptly to pass key reforms to the Violence Against Women Act that bolster indigenous tribes’ ability to prosecute cases involving violence against indigenous women.”

Fortunately, in March of 2013 the Violence Against Women Act (VAWA) was reauthorized to include a provision,
which gave tribal governments criminal jurisdiction over some non-Indians who commit crimes on reservations. This recent legislation is hailed as a victory for indigenous women seeking justice and protection from the legal system, but there are also many critics and notable shortcomings of the new provision. This paper seeks to examine whether the reauthorized Act is truly a victory for Native American women and if it adequately protects their human rights. This study will focus on three key human rights established by the United Nation's Declaration of Human Rights: "the right to life, liberty and the security of person, the right to recognition and equality everywhere as a person before the law, and the right to an effective remedy by the competent national tribunals for acts violating the fundamental rights granted him by the constitution or by law".

HISTORY OF GENDER VIOLENCE AND TRIBAL JURISDICTION

Sexual abuse against Native American women is astonishingly prevalent and particularly violent. According to U.S. Department of Justice, Native American women are more than two and a half times more likely to be raped or sexually assaulted than are other women in the United States. Approximately one in three Native American women will be raped in their lifetimes. This rate is most likely even higher due to the underreporting of sexual violence crimes; according to the Department of Justice, seven percent of sexual assaults against Native American women go unreported. Many of the Native American women interviewed by Amnesty International said they did not know of any women in their community who had not experienced sexual violence. Furthermore, there is evidence that Native American women are more likely than other American women to suffer additional violence at the hands of their attackers. Rapes against Native American women are three times more likely to involve weapons than all other rapes in the United States. In a 2006 study, ninety-six percent of American Indian respondents who had been a victim of rape or sexual assault had experienced other physical abuse as well. Lisa Brunner, the Director of the Sacred Spirits First Nations Coalition and advocate for the survivors of sexual violence in the Native American community, says that rates of rape are so high in her community that girls discuss rape in terms of what to do “when raped,” and not “if [I am] raped.” She recalls what one young girl told her: “My mom and I already talked about that. When I’m raped, we won’t report it, because we know nothing will happen. We don’t want to cause problems for our family.” Sexual assaults are a constant threat and, as illustrated by Lisa Brunner’s experience, a definite reality in native women’s lives.

According to the US Department of Justice, in at least eighty-six percent of the reported cases of rape or sexual assault against Native American women, victims report that the perpetrator is a non-Native man. This represents a substantially higher rate of interracial sexual violence than is experienced by Anglo or African American women within the United States. Reservation demographics are partially responsible for this. A significant portion of residents on most reservations are non-Indians, largely a result of the United States government’s sale of tribal land to white settlers around the turn of the century. More than half of all married Native American women have non-native husbands and, arguably as a consequence, Native American women experience some of the highest domestic-violence victimization rates in the country. However, reports also state that sexual predators from outside tribal lands will often travel to reservations with the intent to rape. Accounts of violence against women living in tribal communities generally increase during hunting season. Historically, Indian tribes have exercised full authority over its inhabitants. Early federal treaties specifically noted a tribe’s power to punish non-Indians. However, towards the end of the nineteenth century, there was a push from the United States government to dismantle tribal government systems. Criminal law enforcement, especially in cases involving non-Indians, became federal or state matters, and tribal court powers became increasingly limited. In 1968, the Indian Civil Rights Act limited the criminal sentences that tribal courts could impose up to one year in jail and a $5,000 fine. To put this restriction into perspective, in cases of rape, state court sentences typically exceed eight years and federal sentences generally surpass twelve. Moreover, in the 1978 case Oliphant v. Suquamish Indian Tribe the Supreme Court ruled it unconstitutional for tribal courts to try non-natives without Congress’ consent. This was an injustice to Indian victims of all crimes, but most exacerbated in regards to gender violence because sexual assaults on Native American women are overwhelmingly intercultural. David Perez, a graduate of Yale Law School and legal commentator, states, “the biggest problem Native American women face isn’t related to crimes committed by Native Americans—it’s crimes committed by non-Indians on tribal land. But those who commit violence against women on tribal lands are robbing this legal maze with absolute impunity.”

Native women who come forward today to report sexual violence are caught in a jurisdictional maze between three justice systems: tribal, state and federal. Whether the victim is a member of a federally recognized tribe, the accused is a member of a federally-recognized tribe, and whether the offense took place on tribal land, are the three most significant deciding factors in determining which justice system has the authority to prosecute the crime. David Perez explains that, “if neither the victim nor the perpetrator is Native American, then only State authorities can make the arrest and try the case. If the victim is Native American, but the perpetrator is not, then only federal agents can make the arrest. And if the victim is not Native American, but the perpetrator is? Then tribal authorities can make the arrest, but only federal courts would have jurisdiction to try the case.” There are often significant delays before police, lawyers, and courts can eventually agree upon who has jurisdiction over a particular crime. There have even been cases where there was so much confusion over jurisdiction that the case was never tried.

The bureaucracy regarding jurisdiction has ultimately led to inefficient law enforcement on tribal lands. According to recent studies, law enforcement on reservations rarely leads to prosecution and conviction of non-Indian offenders. N. Bruce Duthu points out in the New York Times article “Broken Justice in Indian Country” that the “Department of Justice’s own records show that in 2006, prosecutors filed only 566 criminal cases in all of Indian Country.” The Bureau of Indian Affairs, a senior researcher at the Tri-Ethnic Center for Preventative Research, “The message to Native women and their children is that they are expendable and there is no real help or assistance within the system.”

VIOLENCE AGAINST WOMEN ACT

The Violence Against Women Act is a segment of the Violent Crime Control and Law Enforcement Act of 1994. VAWA has been widely credited with helping law enforcement and prosecutors crack down on domestic violence nationwide. The Act provides additional tools for protecting women on Native reservations by defining a new federal habitual-offender crime penalty and authorizing warrants arrests to federal law enforcement officers who determine probable cause during domestic violence cases. VAWA also created the Violence Against Women Office (VAVO), which currently administers 21 grant programs and subsequent legislation, four of which are specifically targeted to Native American populations.

Moreover, federal and state prosecutors often lack the time and resources to pursue cases, and yet they are responsible for all cases involving non-native offenders. According to the Government Accountability Office, between 2005 and 2009, 67 percent of sexual abuse cases sent to the federal government for prosecution were declined. Although the Justice Department claims it has mandated extra training for prosecutors and has directed each field office to develop its own plan to help reduce violence against women, there have been no significant or quantitative improvements in recent years. Some advocates for Native American women say they no longer urge victims to report rapes. Even if a case is accepted by the federal government, relying on federal or state authorities often means having to travel hundreds of kilometers to the nearest forensic examiner or prosecutor. Sarah Deer, an assistant professor of law at William Mitchell College and a citizen of the Menominee Nation of Oklahoma, states: “There’s never really been accountability for non-Indians coming into tribal communities and committing acts of rape or domestic violence; tribal governments can’t prosecute them. I’ve heard tribal police say that the white men on the reservation basically flaunt their violence and take what they can and get away with it. You can’t confine the bounds of the law.” The United States legal system essentially leaves Native American women helpless and vulnerable. According to Colorado State University expert Roe Bubar, an assistant professor in the school of Social Work and Ethnic Studies and Pamela Jumper Thurman, a senior researcher at the Tri-Ethnic Center for Preventative Research, “The message to Native women and their children is that they are expendable and there is no real help or assistance within the system.”

Human Rights Impact

Human Rights Impact

Review

DISCUSSIONS
On March 7, 2012, Congressman Dan Boren introduced the Stand Against Violence and Empower (SAVE) Native Women Act in addition to VAWA. The Act allows tribes to exercise sovereignty in investigating, prosecuting, convicting, and sentencing both Native Americans and non-natives who assault Native American partners in native lands. The reauthorized Act also clarifies tribes’ sovereign power to issue and enforce civil protection orders against natives and non-natives. According to the Act, tribal criminal jurisdiction over non-natives is limited to domestic violence crimes, dating violence, and criminal violations of protection orders. Crimes between two strangers (including sexual assaults), crimes committed by a person who lacks sufficient ties to the tribe, child and elder abuse that does not involve the violation of a protection order, and crimes between two non-natives are still not protected against. In addition to addressing issues of jurisdiction, the SAVE Act requires the Attorney General to submit an annual report of suggestions given by Indian tribes and actions taken to respond to recommendations from years prior. The purpose of these annual reports is to facilitate cooperation and consultation between tribes and law enforcement agencies.

The other major additions to VAWA that the 2013 reauthorization creates, aside from the sovereignty of tribal courts, is the protection against intimate partner violence of lesbian, gay, bisexual, and transgender people and extended access to United States’ visas for immigrant victims. Ultimately, the reauthorized act extends the protections against gender violence to minorities who did not receive the full benefit of the original Violence Against Women Act in 1994.

A strengthened version of the Violence Against Women Act was signed by President Obama on March 7, 2013. It is still hailed as a great victory for Native American women. When President Obama signed the reauthorization, he commented, “This is the day of the advocates, the day of the survivors. This is your victory. This victory shows that the American people make their voices heard, Washington listens.” Native Americans are commonly thought of as the biggest beneficiaries of the reauthorization. “It’s a great victory for women everywhere but especially tribal women,” said Rep. Ani Kerkpatrick. Secretary of the Interior Ken Salazar praised the new Act, stating, “This historic legislation, which recognizes and affirms inherent tribal jurisdiction over non-Indians in domestic violence cases, will provide much needed tools to tribal justice systems to effectively prevent Indian women from abuse.”

The VAWA Reauthorization of 2013 only goes halfway to ensure the human rights of liberty, life and security for person for Native American women. While the new tribal provisions allow Native American communities much more sovereignty than previous versions of VAWA, there are still extreme jurisdictional limitations. For example, crimes between two strangers (including sexual assaults), crimes committed by a person who lacks sufficient ties to the tribe (e.g. living or working on its reservation), and child or elder abuse that does not involve the violation of a protection order are still out of tribal courts’ jurisdiction. Sarah Deer, a citizen of Muscogee Creek Nation and assistant law professor at William Mitchell College of Law, explains that the law will only apply to non-Indians who are married or in an intimate relationship with a tribal member, and it is limited to cases of domestic violence. Bruce Duscha, an internationally recognized scholar of Native American law and professor at Dartmouth College, points out that “The reauthorized VAWA goes part of the way by affirming tribal sovereignty over all offenders for a very limited class of offenses.”

Furthermore, while the VAWA reauthorization gives tribal courts more sovereignty, it does nothing to address the concerning inequities of tribal courts. According to Amnesty International, “Tribal law enforcement agencies are also chronically under-funded and federal and state governments provide significantly fewer resources for law enforcement on tribal land than they provide for comparable non-Native communities. The lack of appropriate training in all police forces—federal, state and tribal—also undermines survivors’ right to justice.” Tribal courts’ recently enlarged jurisdiction is currently regarded as a great victory, but it is important to remember that these tribal law enforcement systems do not presently have the necessary means to successfully pursue justice for victims.

Futhermore, tribes yearning to take advantage of VAWA’s jurisdictional provisions must first enact many institutional changes, including amending current tribal codes, hiring new judges, and devoting resources to pay for public defenders. Thus, the VAWA reauthorization does not ensure American women’s right to recognition and equality everywhere as a person before the law. It is undeniable that Native American women still receive substandard legal protection and security compared to the protections other American women receive.

As decreed by the United Nations, it is a human right to “an effective remedy by the competent national tribunals for acts violating the fundamental rights granted him by the constitution or by law.” The federal advisory bodies, equivalent to “national tribunals,” suggested that federal agencies responsible for investigating and prosecuting sexual violence in Indian Country need to prioritize these cases and improve the transparency of their processes. The councils also recommended that tribal authorities have jurisdiction over non-Native offenders in Indian Country. According to the White House, most of the committees’ suggestions are included in the reauthorized version of the Violence Against Women Act. However, the reauthorized Act does not dictate any necessary requirement for federal agencies to make sexual violence cases on tribal lands a priority.

Furthermore, tribal authorities only have jurisdiction over some of the non-native offenders on tribal lands. Ultimately, Native Americans were not granted the full “effective remedy” that these interagency councils recommended.

Another major limitation of the 2013 VAWA reauthorization is that Alaskan Native women are left out. As Native Americans and supporters across the country celebrate this victory, the media has largely ignored the controversial provision that excluded Alaskan Native tribes from the tribal jurisdiction provisions. This new provision prevents Alaskan Native women from gaining the same benefits that all other Native American women in the United States now receive from the VAWA reauthorization. The cause of this disparity between Alaska Natives and Native Americans is differences in land ownership in Alaska, tribes do not have reservations, so they cannot base claims of jurisdiction on reservation boundaries. Tragically, for the same reason, Native Alaskan women are probably in the most need of tribal sovereignty. There are currently 140 Alaskan villages with no state law enforcement. Because of the vast distances, weather conditions, and lack of state trooper posts in Alaska, law enforcement response times can be very slow to help. The only place many women can turn to for protection against gender violence is their tribe. Thus, Native Alaskan women’s human rights continue to be grossly violated.

RECOMMENDATIONS

In order to best protect Native American women’s human rights, VAWA needs to extend tribal jurisdiction to all crimes of gender violence that occur on tribal lands. As sovereign entities closest in physical distance to the actual crime, tribal courts are likely to be the most effective means of law enforcement and thus able to engage the community in efforts to prevent gender violence in the first place. Tribal courts undeniably care more about the wellbeing of victims, and the argument that tribal courts are incapable of producing impartial juries is unfair and discriminatory. Moreover, Native American tribes are privy to the collective human right of governing themselves, as decreed by the United Nations as, “indigenous peoples, in exercising their right to self-determination, have the right to autonomy or self-government in matters relating to their internal and local affairs.” In my opinion, a crime of gender violence which occurs on tribal land is an internal matter, no matter whether the offender is native or not. The loopholes in the justice system concerning the prosecution of non-natives are precisely what perpetuate the culture of rape on tribal reservations. In order to dismantle this cultural norm of sexual assault, it is critical that more federal funds from VAWA should go towards improving the tribal courts and law enforcement system so that they are actually effective.

I also recommend that tribal court systems create stronger state/tribal relationships. Sarah Deer states that “during the last century, various criminal codes have been written and signed into law by tribal legislatures—some much better than others. Statutes are sometimes out of date. In addition, some of the earliest tribal criminal codes were taken from “boilerplate” codes which were drafted by non-Indians. Over the past several years, she has reviewed over 100 tribal sexual assault laws. What [she has] found is that many tribal codes have weaknesses—and most of the time, these weaknesses are inconsistent with tribal traditional laws which served to protect women and children.” For example, some tribal codes require that a prosecutor prove that physical force was
used to commit sexual assault and some even have a marital exemption clause. These standards of gender violence are outdated and, frankly, insulting to women. The sovereignty of tribal courts can only benefit Native American women if tribal laws are updated to efficiently protect native women's human rights. If there is no sexual assault code in place at the tribal level, no justice can be found in tribal court.

Furthermore, in order to equalize the treatment of Native American women and non-native women before the law, it is imperative to create a system to collect, analyze and disseminate crime and victimization data on tribal lands.

There is currently no systematic national data collection effort focused on crime on reservations, whereas there are extensive programs for this purpose throughout the rest of the United States. It is very rare that federal, state, and local crime data reports even distinguish between offenses committed in Indian Country from those committed elsewhere. According to the National Institute of Justice’s Program of Research on Violence Against American Indian and Alaska Native Women, “The primary mechanisms for reporting crime data—the FBI’s Uniform Crime Reporting (UCR) program and the National Incident Based Reporting System (NIBRS)—do not include offenses committed on reservations or criminal and delinquency arrests and subsequent processing by federal agents (e.g., FBI, BIA, The Drug Enforcement Administration [DEA], Bureau of Alcohol, Tobacco, Firearms and Explosives [ATF], U.S. Immigration and Customs Enforcement [ICE]).” Collecting such information allows the government to anticipate, monitor, and prevent such criminal activity. The next VAWA reauthorization should create such a system so that Native American women can finally begin to receive the same protection against gender violence that all other American women receive.

Ultimately, it is important to remember that the condition of Native American women today can be explained through history. The high rate of gender violence experienced by native women today at the hands of white men is almost a tradition of American society. In order to truly change such an ingrained problem, the attitude of an entire nation must be reformed. The VAWA reauthorization of 2013 represents a step in the right direction, but there is still much more to be done to safeguard native women’s human rights.

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Melanie DeArdo, RN, BSN, graduated from Capital University in 2013. She currently is a staff RN at Texas Children’s Hospital on the Progressive Care Unit.

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Nicholas Novak is a senior Integrated Graduate Studies student in Anthropology with a double major in Medical Anthropology and Evolutionary Biology at Case Western Reserve University. In his spare time, he is an officer in Mortar Board, an ELP Mentor and a volunteer at University Hospitals Seidman Cancer Center.

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So Hee Moon is a sophomore from West Chester, PA majoring in Chemical Biology at Case Western Reserve University with a strong science, liberal arts, and experiential fund of knowledge. Her academic interests include genetics, disease, and organic chemistry. So Hee loves getting involved on campus through her activities as a peer tutor, a SELP mentor for Educational Service for Students (ESS), and a president of Carlton Road Community Council for Residence Hall Association (RHA). Currently, she works in Dr. Lederman’s lab studying latent reservoirs of HIV. As a student in the 6-year Pre-Professional Scholars Program in Dentistry, she aspires to become an orthodontist in the future.

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Katrina Thede is a senior Biology and Music major at Case Western Reserve University. Her future plans after graduation are to attend medical school and continue doing research in order to help create new technologies to better treat patients and cure diseases.

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Lauren Kelly is a junior at Duke University. She is majoring in Public Policy and hopes to attend law school after graduation. She has interned at New York City’s Office of Emergency Management and the Women’s Legal Centre in Cape Town, South Africa. She is the Director of the student-run non-profit North Carolina Common Sense, co-chair of the Student Advisory Board to Duke’s Human Rights Center and a member of the Duke Dance Marathon committee. She is a member of the Kappa Alpha Theta Sorority. This paper served as her final culminating project for the Duke University program “Duke Immerse: Rights and Identities in the Americas.” She would like to thank her faculty advisors, Robin Kirk and Robert Korstad, for an incredibly transformative and enlightening Duke Immerse experience.
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